Remarks

The Rejection of Claims 25-32 Under U.S.C. § 112, First Paragraph

Claims 25-32 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. The rejection is respectfully traversed.

Claim 25 is the independent claim of the rejected claim set. Claim 25 recites a method of screening compounds to identify candidate anti-cancer agents. A cell that has a genetic alteration which dysregulates *c-MYC* expression is contacted with a test compound. The genetic alteration causes *c-MYC* overexpression. The CDK4 kinase activity of the cell is measured. A test compound which inhibits CDK4 kinase activity is identified as a candidate agent with anti-cancer activity.

To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

The Patent Office asserts that the step of "measuring CDK4 kinase activity of the cell" is not enabled. Although applicants have made eight references of record to demonstrate that methods of "measuring CDK4 kinase activity of a cell" were well known in the art at the time the application was filed, the Patent Office maintains the enablement rejection. Some of these references teach measurement of CDK4 kinase activity of a cell by quantitating pRB protein phosphorylation in cells contacted with agents. Others teach immunoprecipitating CDK4 from cells contacted with agents and measuring *in vitro* phosphorylation of purified pRB by the immunoprecipitated CDK4. In the final Office Action and the interview with examiners Yu and

Mosher on June 2, 2003 the Patent Office explained that the step of measuring CDK4 kinase activity of the cell remains not enabled because it is unclear whether immunoprecipitated CDK4 kinase activity reflects CDK4 kinase activity in an agent-treated cell. The Examiners expressed concern that the inhibitor would be removed from CDK4 during the immunoprecipitation and therefore the assay would not be able to identify any inhibitors.

CDK4 immunoprecipitation (IP) assays were known at the time the application was filed to be useful for identifying agents that alter CDK4 kinase activity of cells. Exhibits A-F demonstrate identification of agents that inhibit or enhance CDK4 kinase activity of a cell using the CDK4 IP assay. Each Exhibit teaches that a cell was contacted with an agent. Cells contacted with the agent had increased or decreased CDK4 kinase activity in a CDK4 IP assay relative to cells not contacted with the agent. However, CDK4 expression was unchanged in cells contacted and not contacted with the agent. Thus the difference in CDK4 kinase activity of the cells was attributed to the agents' ability to affect the cells' CDK4 kinase activity.[1]

Li *et al.* (*Experimental Cell Research* (1999) *253*, 372-384; attached as Exhibit A; previously made of record in the response to Office Action dated January 21, 2003) measured CDK4 kinase activity of a cell contacted with retinoid molecules using the IP assay. (Page 374, column 1, lines 24-41.) Li found, "Cdk4 protein levels did not change appreciably following any treatment [with a retinoid]." (Page 380, column 1, line 11-12.) Although the CDK4 protein levels in the cells treated with retinoid were unchanged, CDK4 kinase activity of the cells decreased. Li teaches, "In extracts prepared from all-*trans*-RACT [retinoic acid and theophylline]-treated cells, the amount of Cdk4-dependent kinase activity was 50% that observed

[1] Exhibits B-F are first made of record in response to the final Office Action. These Exhibits are directed solely to issues that were newly raised in the final Office Action and the interview with Examiners Yu and Mosher. Thus, applicants respectfully request consideration of Exhibits B-F.

in cells treated with CT [theophylline] alone." (Page 380, column 1, line 24 to column 2, line 2.) Thus Li teaches use of the CDK4 IP assay to measure the effect of an agent on CDK4 kinase activity of a cell.

Sun *et al.* (*J. Biol. Chem.* (1999) *274*, 6930-6934; Exhibit B) measured CDK4 kinase activity of a cell contacted with geranylgeranyltransferase inhibitor GGTI-298 using an immunoprecipitation assay. (Page 6931, column 2, lines 32-42.) The cells contacted with GGTI-298 expressed CDK4 at the same level as cells that were not contacted with GGTI-298. "Treatment of Calu-1 cells with GGTI-298 did not alter the levels of CDK2 and CDK4 or those of cyclins E and D1." (Page 6932, column 1, lines 23-25.) However, the cells contacted with GGTI-298 exhibited decreased CDK4 activity. "Treatment with GGTI-298 blocked the activity of CDK2, inhibited CDK4 and CDK6 activities by 75% and 30%, respectively." (Page 6932, column 1, lines 9-11.) Thus, Sun teaches that the CDK4 IP assay identified an agent as altering CDK4 kinase activity of a treated cell.

Taulés *et al.* (*J. Biol. Chem.* (1998) *273*, 33279-33286; Exhibit C) measured the affect of anti-calmodulin drugs (*e.g.*, W13) on CDK4 kinase activity of rat kidney cells using the IP assay. (Page 33280, column 1, line 68 to column 2, line 27.) In both cells contacted with W13 and cells not contacted with W13 CDK4 expression levels were the same. Taulés teaches that "the addition of W13 to cultures at 5 h after activation induced a decrease of the amount of cyclin A, whereas the levels of Cdk4, Cdk2, cyclin D, and cyclin E were not affected." (Page 33282, column 1, lines 27-29.) Although CDK4 expression levels were the same in W13 treated and untreated cells, CDK4 kinase activity was diminished in the cells contacted with W13. "The activities of both Cdk4 and Cdk2 in W13-treated cells were much lower than in control cells at all the times studied." (Page 33281, column 2, line 6 to page 33282, column 1, line 1.) Thus

Taulés identified an agent that affected CDK4 kinase activity of a treated cell using a CDK4 IP assay.

Servant *et al.* (*J. Cell Biol.* (2000) *148*, 543-556; Exhibit D) determined the effect of platelet-derived growth factor-BB (PDGF-BB) and angiotensin II (Ang II) on CDK4 kinase activity in cultured aortic smooth muscle cells (SMC) using the CDK4 IP assay. (Page 545, column 2, lines 15-36.) In SMCs treated with either PDGF-BB or Ang II, CDK4 expression levels were unchanged. "Little difference was observed in the expression level of the catalytic subunits Cdk4 and Cdk2." (Page 547, column 2, lines 7-8.) CDK4 kinase activity in the treated cells, however, was increased compared to untreated cells. "Both Ang II and PDGF-BB increased the Rb kinase activity of Cdk4, which became detectable at eight hours and remained elevated up to the end of G_1 phase." (Page 548, column 1, line 9 to column 2, line 3.) Thus, Servant teaches that the CDK4 IP assay can detect changes in CDK4 kinase activity of a cell treated by an agent.

Wang *et al.* (*Cell Growth and Differentiation* (1996) *7*, 1471-1476; Exhibit E) examined CDK4 kinase activity of mouse myoblast C2C12 cells that were shifted from growth medium to differentiation medium using the CDK4 IP assay. (Page 1477, column 2, line 68 to page 1478, column 1, line 25.) Wang discovered that expression levels of CDK4 activity were unchanged in cells incubated in growth medium relative to differentiation medium. "CDK4 and CDK6 protein levels remained constant during myocyte differentiation." (Page 1472, column 1, lines 25-26.) Although CDK4 protein expression levels were unchanged in the cells, CDK4 activity was diminished.

> To investigate the mechanisms that may contribute to the observed changes in Rb phosphorylation during C2C12 myogenesis, the *in vitro* Rb kinase activities of CDK4, cyclin D1, and cyclin D3

> immunoprecipitates were determined using a GST-Rb fusion protein as substrate. Relatively high levels of Rb kinase activities were detected in all immunoprecipitates from myoblast cell lysates, whereas these Rb kinase activities were considerably lower in cell lysates prepared from myotubes and myotubes restimulated with serum.

Page 1472, column 2, lines 18-27. Thus Wang teaches identification of an agent that alters CDK4 kinase activity of a treated cell using the CDK4 IP assay.

Tsihlias *et al.* (*Oncogene* (2000) *19*, 670-679; Exhibit F) measured the effect of dihydrotestosterone (DHT) on CDK4 activity of a human prostate carcinoma cell line, LNCaP, using an IP assay. (Page 677, column 2, lines 10-16.) No change in level of expression of CDK4 was observed in cells that were contacted with DHT versus cells that were not contacted with DHT. "There was no appreciable change in the protein levels of cdk2, cdk4, and cdk6, cyclins D1 and E, or the cdk inhibitors $p16^{INK4A}$ and $p21^{Cip1}$." (Page 672, column 2, lines 12-14.) Kinase activity of CDK4 in the cells, however, was decreased in cells treated with DHT relative to untreated cells. Tsihlias teaches, "Cdk4 activity was strongly inhibited by treatment of 100 nM DHT." (Page 673, column 2, lines 17-18.) Thus Tsihlias teaches identification of an agent that affects CDK4 activity of a cell using the CDK4 IP assay.

Exhibits A-F demonstrate that IP assays can indeed be used for determining CDK4 kinase activity of a cell. Contrary to the assertion of the Patent Office, the IP assay does not separate all inhibitors from CDK4. Thus IP is a useful assay for measuring CDK4 activity in a cell. Thus, one of skill in the art could have readily performed the step of "measuring CDK4 kinase activity of the cell" as recited in claims 25-32 without having to resort to undue experimentation. The specification enables one of skill in the art to practice the invention.

Applicants respectfully request withdrawal of this rejection to claims 25-32.

The Rejection of Claims 25-32 Under 35 U.S.C. § 112, Second Paragraph

Claims 25-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse.

The Office Action asserts that claims 25-32 are indefinite because they recite a step of measuring CDK4 activity, but "[t]he specification does not teach any method directly measuring the CDK4 kinase activity." (Paper 15, page 2, lines 18-19.)[2]

Rejections under 35 U. S.C. § 112, second paragraph, are based on whether the scope of the claims is sufficiently clear that the public is informed of the boundaries of what constitutes infringement of the patent. See MPEP § 2173. The Office Action asserts no reason why the scope of the claims is unclear. Rather, the Office Action asserts that the *specification* does not teach *how to* measure CDK4 kinase activity of a cell. ("The specification does not teach any method directly measuring the CDK4 kinase activity." Paper 15, page 2, lines 18-19.) This assertion appears to concern the enablement requirement of 35 U.S.C. § 112, first paragraph.[3] The rejection is as presented improper.

Applicants respectfully request withdrawal of this rejection to claims 25-32.

Objection of the Specification

The specification has been objected to for improper incorporation of essential material by reference to a foreign application or patent, or to a publication. Specifically, the Office Action asserts:

[2] The step of "measuring CDK4 kinase activity of the cell" does not require that the CDK4 kinase activity of the cell be *directly* measured. The step only requires that the CDK4 kinase activity possessed by the cell be measured.
[3] The enablement of claims 25-32 has been discussed, above.

> How to measure activity of CDK4 is essential to practice the instantly claimed invention and [the] only teaching in the specification [of] how to measure the activity is at page 9 lines 1 and 2, a reference to Li et al and the Office maintains this reference to a publication of essential ma `terial in the specification by reference to a foreign application or patent, or to a publication is improper.

Paper 15, page 2, lines 6-11. Applicants respectfully traverse that this subject matter is essential.

As discussed above with regard to the enablement requirement of 35 U.S.C. § 112, first paragraph, CDK4 kinase assays were well known in the art at the time the application was filed. See references submitted on January 21, 2003 with the prior response to Office Action. Since those of skill in the art could have readily found such assays in many articles in the scientific literature, the Li reference is not essential to the practice of the invention.

Thus the citation of Li is not improper because it is not essential.

Applicants respectfully request withdrawal of this objection.

Respectfully submitted,

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